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Efficient synthesis of anthranilic esters *via* Pd-catalyzed dehydrogenative/decarbonylative coupling of anilides and glyoxylates†

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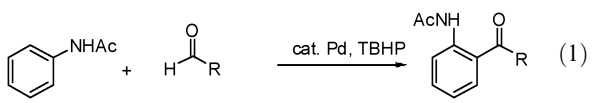
A novel way of synthesizing anthranilic esters was developed *via* Pd-catalyzed dehydrogenative/decarbonylative coupling between anilides and glyoxylates.

Recently transition metal catalyzed C–H activation of arenes has been successfully developed as a valuable tool for the synthesis of a large variety of structurally diverse molecules.[1,2] Among the various metal catalysts employed, palladium has been shown to be the most versatile catalyst for the installation of functional groups such as halogen,[3] hydroxy,[4a] alkoxy,[4b] acetoxy[5] and amino[6] groups on the arenes through C–C and C–X bond formations. Besides these functional groups, the installation of carbonyl groups on the arenes, *i.e.*, the synthesis of aryl ketones and carboxylates from benzene derivatives *via* Pd-catalyzed dehydrogenative coupling has been an area of intensive research.[7–9] For example, Li and others reported dehydrogenative couplings between 2-aryl pyridines and aryl aldehydes to produce aryl ketones.[7a,b] Later on, Kwong *et al.*[7c] successfully extended this protocol to the dehydrogenative coupling between acetanilides and aryl aldehydes. Even more impressive is that Li and Deng were able to successfully use alcohols instead of aldehydes in the couplings, thus increasing the overall reaction efficiency further.[8] While various protocols based on Pd-catalyzed C–H activation of arenes have been developed for the synthesis of aryl ketones from benzene derivatives, only few methods are known to produce aryl carboxylates.[10] Herein we report that anthranilic esters can be efficiently synthesized *via* Pd-catalyzed dehydrogenative/decarbonylative coupling between anilides and glyoxylates.

Inspired by Li and Kwong's results that, using TBHP as the oxidant, aldehydes can undergo Pd-catalyzed dehydrogenative coupling with anilides to produce aryl ketones eqn (1), we envisioned that phenylglyoxylate can be generated in a similar fashion if the aldehydes are replaced with glyoxylates eqn (2).



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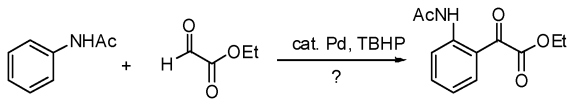
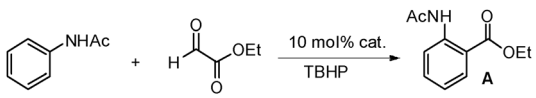


(2)

When acetanilide was heated with 2 equiv. of ethyl glyoxylate and 4 equiv. of TBHP in the presence of 10 mol% of $Pd(OAc)_2$ in benzene at 120 °C for 16 h, much to our surprise, we found that the product isolated in 19% yield was actually ester **A**, an anthranilic ethyl ester, not the expected ethyl phenylglyoxylate (Table 1, entry 1). Somehow a decarbonylation has taken place during the reaction to produce the ester **A**. Since two hydrogen atoms and one molecule of CO were lost in the process, this reaction can be formally viewed as a Pd-catalyzed dehydrogenative/decarbonylative coupling between anilides and ethyl glyoxylate. When the Pd catalyst was switched to $PdCl_2$, the yield dropped to 12% while the use of $Pd(TFA)_2$ increased the yield substantially to 29% (Table 1, entries 2 and 3). The use of polar solvents such as DMF or DMSO shuts down

Table 1 Reaction conditions optimization



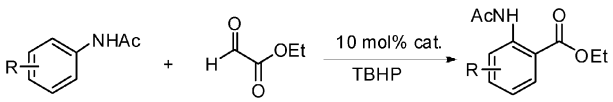
Entry	Catalyst	Temp (°C)	Ligand/additive	Solvent	Yield[a] (%)
1	$Pd(OAc)_2$	120	—	Benzene	19
2	$PdCI_2$	120	—	Benzene	12
3	$Pd(TFA)_2$	120	—	Benzene	29
4	$Pd(TFA)_2$	120	—	Toluene	32
5	$Pd(TFA)_2$	120	—	DMF	0
6	$Pd(TFA)_2$	120	—	DMSO	0
7	$Pd(TFA)_2$	130	—	Toluene	30
8	$Pd(TFA)_2$	120	AgOAc	Toluene	28
9	$Pd(TFA)_2$	120	PPh_3	Toluene	41
10	$Pd(TFA)_2$	120	dppe	Toluene	40
11	$Pd(TFA)_2$	120	dppb	Toluene	34
12	$Pd(TFA)_2$	120	1,10-Phen	Toluene	30
13	$Pd(TFA)_2$	120	dppf	Toluene	42
14	*$Pd(TFA)_2$*	*120*	*dppp*	*Toluene*	*55*
15	*$Pd(TFA)_2$*	*120*	*dppp*	*Toluene*	*66*
16	—	120	dppp	Toluene	0

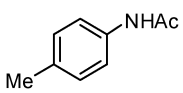
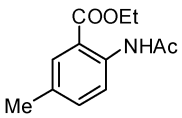
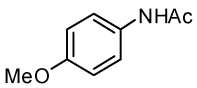
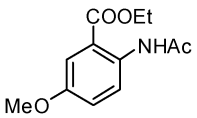
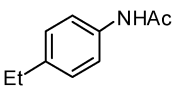
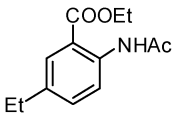
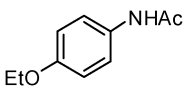
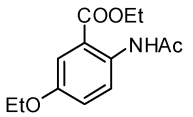
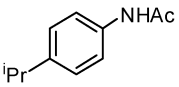
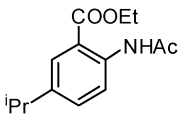
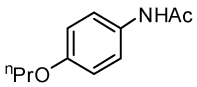
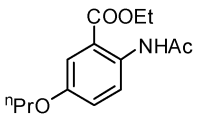
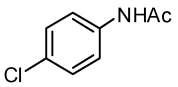
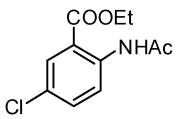
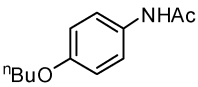
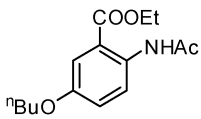
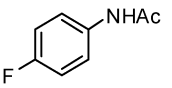
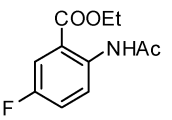
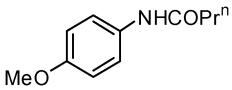
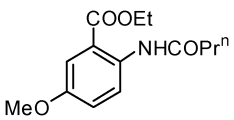
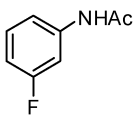
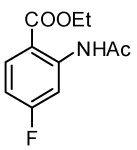
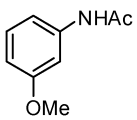
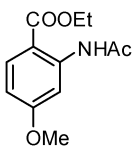
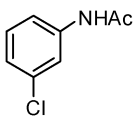
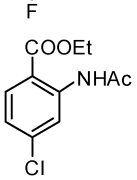
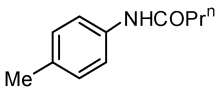
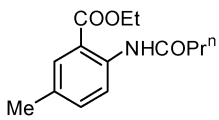
Reaction conditions: anilide (1 equiv.), Pd-catalyst (10 mol%), TBHP (4 equiv.), glyoxylate (2 equiv.), solvent (2 mL $mmol^{-1}$), under N_2, ligand (10 mol%), 16–24 h. [a] Isolated yields. [b] The reaction was stopped after 12 h and another 5 mol% of Pd catalyst was added.

the reaction completely (Table 1, entries 5 and 6). When the solvent was changed to toluene, the yield was improved slightly to 32% (Table 1, entry 4). Increasing the reaction temperature to 130 °C or adding AgOAc as an additive all had little effect on the reaction yield (Table 1, entries 7 and 8). Gratifyingly, extensive tests showed that adding phosphine compounds as additives benefited the reaction. It was discovered that dppp gave the best yield (55%) whereas other ligands such as PPh_3, dppe, dppb, dppf or N-based ligand 1,10-phen are less effective (Table 1, entries 9–14). This yield can be further improved to 66% if the reaction was stopped after 12 h and another batch of Pd-catalysts was readded (Table 1, entry 15). Since these phosphine compounds can be oxidized to phosphine oxides by TBHP in the reaction, the true nature of the ligand is still unknown at present. However, the benefit of adding a suitable bidentate phosphine ligand was also observed in Li's reaction.[8b] The test also showed that the use of triphosphine oxide did not benefit the reaction. Control reaction also showed that the Pd-catalyst was necessary for the reaction to proceed (Table 1, entry 16). On the basis of the above results, we decided to set reaction of 2 equiv. of ethyl glyoxylate with 1 equiv. of anilide and 4 equiv. of TBHP in the presence of 10 mol% of $Pd(TFA)_2$ and 10 mol% of dppp in toluene at 120 °C as our standard protocol.

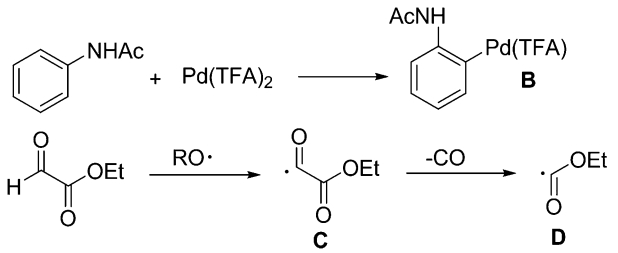
With the optimized protocol in hand, we next set out to explore the scope and limitation of the reaction and the results are summarized in Table 2. We found that the reaction worked satisfactorily when substituents such as methyl, ethyl and isopropyl groups were placed on the aromatic ring, affording the desired anthranilic ester derivatives in yields around 60% (Table 2, entries 1–3). Substrates with halide substituents were viable coupling partners too. However, their reaction yields dropped to below 50% (Table 2, entries 4–7) if a chlorine or fluorine atom was placed at the 3- or 4-position of the anilide. On the other hand, alkoxy groups such as methoxy, ethoxy, ^{n}PrO- and ^{n}BuO-groups were well tolerated on the anilides and

Table 2 Synthesis of anthranilic esters *via* Pd-catalyzed dehydrogenative/decarbonylative coupling between anilides and glyoxylates



Entry	Anilide	Product	Yield[a] (%)	Entry	Anilide	Product	Yield[a] (%)
1			60	8			63
2			61	9			62
3			62	10			58
4			41	11			54
5			40	12			45
6			41	13			51
7			49	14			47

Reaction conditions: anilide (1 equiv.), Pd-catalyst (10 mol%), TBHP (4 equiv.), solvent (2 mL $mmol^{-1}$), under N_2, dppp (10 mol%), 120 °C, 16–24 h. [a] Isolated yields.



Scheme 1 Possible reaction mechanism.

their couplings with ethyl glyoxylate gave the desired anthranilic esters in yields ranging from 51–63% (Table 2, entries 8–11). It should be noted that when a substituent was placed at the 3-position of the anilide, the coupling only took place on the less hindered side, clearly due to the steric hindrance of the two existing substituents (Table 2, entries 6, 7 and 13). When the acetyl group on the amide was replaced with a propionyl group, the yields of the couplings also dropped to around 45% (Table 2, entries 12 and 14).

Though the exact mechanism is still not clear at present, some information has been gathered. When free radical scavenger BHT was added to the reaction mixture, the reaction was almost completely stopped, suggesting that this reaction may involve a radical intermediate. This observation is consistent with what was reported by others.[8b] On the other hand, the usually invoked palladation-addition to the carbonyl group-dehydropalladation mechanism cannot explain the loss of one molecule of CO during the reaction. We reasoned that the reaction may be initiated with the Pd(II)-mediated *ortho*-palladation of the acetanilide to form intermediate **B** (Scheme 1). TBHP was decomposed into alkoxy radicals which subsequently abstracted the hydrogen off the ethyl glyoxylate to form radical intermediate **C**. At elevated temperature, intermediate **C** lost one molecule of CO to give intermediate **D**. **D** then reacted with intermediate **B** to produce the desired anthranilic ethyl ester through either a Pd(IV)[11] or Pd(III)[12] intermediate. This proposal is supported by the observation that when ethyl formate instead of ethyl glyoxylate was reacted with acetanilide under our standard reaction conditions, the desired anthranilic ethyl ester could be isolated in 13% yield. Possibly these two reactions shared the same reaction intermediates such as **B** and **D**. Since not much is known about the reaction, other mechanisms may be operative here too and a Pd(II) intermediate cannot be completely ruled out.

In summary, a novel way of converting anilides into anthranilic ethyl esters was developed *via* Pd-catalyzed dehydrogenative/decarbonylative coupling between anilides and ethyl glyoxylate using TBHP as the oxidant. The reaction was found to be best run in toluene using $Pd(TFA)_2$–dppp as the catalyst combination. A variety of substituted anthranilic ethyl esters were synthesized in yields of 40–66% and substituents such as alkyl, chloro, fluoro and alkoxy groups are well tolerated on the anilides. This method could be complementary to the carbonylation route for the synthesis of anthranilic acid derivatives from anilides.[10a] Currently efforts are underway to elucidate the reaction mechanism and the results will be reported in due course.

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Notes and references

1 (*a*) G. Dyker, *Handbook of C–H Transformations: Applications in Organic Synthesis*, Wiley-VCH, Weinheim, 2005; (*b*) J. Q. Yu and Z. J. Shi, *C–H Activation*, Springer, Berlin, Germany, 2010.
2 For recent reviews, see: (*a*) C.-L. Sun, B.-J. Li and Z.-J. Shi, *Chem. Rev.*, 2011, **111**, 1293; (*b*) F. Bellina and R. Rossi, *Chem. Rev.*, 2010, **110**, 1082; (*c*) I. A. I. Mkhalid, J. H. Barnard, T. B. Marder, J. M. Murphy and J. F. Hartwig, *Chem. Rev.*, 2010, **110**, 890; (*d*) T. W. Lyons and M. S. Sanford, *Chem. Rev.*, 2010, **110**, 1147; (*e*) O. Daugulis, H.-Q. Do and D. Shabashov, *Acc. Chem. Res.*, 2009, **42**, 1074; (*f*) X. Chen, K. M. Engle, D.-H. Wang and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2009, **48**, 5094; (*g*) F. Kakiuchi and N. Chatani, *Adv. Synth. Catal.*, 2003, **345**, 1077; (*h*) A. R. Dick and M. S. Sanford, *Tetrahedron*, 2006, **62**, 2439; (*i*) J. Q. Yu, R. Giri and X. Chen, *Org. Biomol. Chem.*, 2006, **4**, 4041; (*j*) D. Alberico, M. E. Scott and M. Lautens, *Chem. Rev.*, 2007, **107**, 174; (*k*) L. Ackermann, R. Vicente and A. R. Kapdi, *Angew. Chem., Int. Ed.*, 2009, **48**, 9792; (*l*) L.-M. Xu, B.-J. Li, Z. Yang and Z. J. Shi, *Chem. Soc. Rev.*, 2010, **39**, 712; (*m*) J. Wencel-Delord, T. Droge, F. Liu and F. Glorius, *Chem. Soc. Rev.*, 2011, **40**, 4740.
3 (*a*) T.-S. Mei, D.-H. Wang and J.-Q. Yu, *Org. Lett.*, 2010, **12**, 3140; (*b*) X. Wang, T.-S. Mei and J.-Q. Yu, *J. Am. Chem. Soc.*, 2009, **131**, 7520; (*c*) T.-S. Mei, R. Giri, N. Maugel and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2008, **47**, 5215; (*d*) K. S. L. Chan, M. Wasa, X. Wang and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2011, **50**, 9081; (*e*) D. Kalyani, A. R. Dick, W. Q. Anani and M. S. Sanford, *Org. Lett.*, 2006, **8**, 2523; (*f*) K. L. Hull, W. Q. Anani and M. S. Sanford, *J. Am. Chem. Soc.*, 2006, **128**, 7134; (*g*) X. Wan, Z. Ma, B. Li, K. Zhang, S. Cao, S. Zhang and Z. Shi, *J. Am. Chem. Soc.*, 2006, **128**, 7416.
4 (*a*) Y.-H. Zhang and J.-Q. Yu, *J. Am. Chem. Soc.*, 2009, **131**, 14654; (*b*) X. Wang, Y. Lu, H.-D. Dai and J.-Q. Yu, *J. Am. Chem. Soc.*, 2010, **132**, 12203.
5 (*a*) C. Vickers, T.-S. Mei and J.-Q. Yu, *Org. Lett.*, 2010, **12**, 2511; (*b*) M. H. Emmert, A. K. Cook, Y. J. Xie and M. S. Sanford, *Angew. Chem., Int. Ed.*, 2011, **50**, 9409; (*c*) A. R. Dick, K. L. Hull and M. S. Sanford, *J. Am. Chem. Soc.*, 2004, **126**, 2300.
6 (*a*) T.-S. Mei, X. Wang and J.-Q. Yu, *J. Am. Chem. Soc.*, 2009, **131**, 10806; (*b*) J.-J. Li, T.-S. Mei and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2008, **47**, 6452; (*c*) E. J. Yoo, S. Ma, T.-S. Mei, K. S. L. Chan and J.-Q. Yu, *J. Am. Chem. Soc.*, 2011, **133**, 7652; (*d*) K. Ng, A. S. C. Chan and W.-Y. Yu, *J. Am. Chem. Soc.*, 2010, **132**, 12862.
7 (*a*) O. Basle, J. Bidange, Q. Shuai and C.-J. Li, *Adv. Synth. Catal.*, 2010, **352**, 1145; (*b*) X. Jia, S. Zhang, W. Wang, F. Luo and J. Cheng, *Org. Lett.*, 2009, **11**, 3120; (*c*) Y. Wu, B. Li, F. Mao, X. Li and F. Y. Kwong, *Org. Lett.*, 2011, **13**, 3258.
8 (*a*) F. Xiao, Q. Shuai, F. Zhao, O. Baslé, G. Deng and C.-J. Li, *Org. Lett.*, 2011, **13**, 614; (*b*) C. A. Correia, L. Yang and C.-J. Li, *Org. Lett.*, 2011, **13**, 4581.
9 P. Fang, M. Li and H. Ge, *J. Am. Chem. Soc.*, 2010, **132**, 11898.
10 (*a*) R. Giri, J. K. Lam and J.-Q. Yu, *J. Am. Chem. Soc.*, 2010, **132**, 686; (*b*) R. Giri and J.-Q. Yu, *J. Am. Chem. Soc.*, 2008, **130**, 14082; (*c*) Y. Lu, D. Leow, X. Wang, K. M. Engle and J.-Q. Yu, *Chem. Sci.*, 2011, **2**, 967; (*d*) W.-Y. Yu, W. N. Sit, K.-M. Lai, Z. Zhou and A. S. C. Chan, *J. Am. Chem. Soc.*, 2008, **130**, 3304.
11 (*a*) N. R. Deprez and M. S. Sanford, *J. Am. Chem. Soc.*, 2009, **131**, 11234; (*b*) J. M. Racowski, A. R. Dick and M. S. Sanford, *J. Am. Chem. Soc.*, 2009, **131**, 10974.
12 (*a*) D. C. Powers and T. Ritter, *Nat. Chem.*, 2009, **1**, 302; (*b*) D. C. Powers, M. A. L. Geibel, J. E. M. N. Klein and T. Ritter, *J. Am. Chem. Soc.*, 2009, **131**, 17050.